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AN OVERVIEW ON NON-T CELL PATHWAYS IN TRANSPLANT REJECTION AND TOLERANCE

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Abstract

Purpose of review—Recent studies have demonstrated unexpected roles for non-T cells, especially innate immune cells, in the regulation of transplant outcomes. In this review, we highlight our recent understanding on the role of NK cells, dendritic cells, and macrophages in the allograft response, and discuss whether such cells can be targeted for the induction of transplant tolerance.

Recent findings—There are unexpected roles for non-T cells in regulating transplant outcomes, and depending on the models and tolerizing protocols, the innate immune cells contribute significantly to both graft rejection and graft acceptance. Some innate immune cells are potent inflammatory cells directly mediating graft injury, while others regulate effector programs of alloreactive T cells and ultimately determine whether the graft is rejected or accepted. Furthermore, when properly activated, some innate immune cells promote the induction of Foxp3+ Tregs whereas others efficiently kill them, thereby differentially affecting the induction of tolerance. These new findings unravel unexpected complexities of non-T cells in transplant models and may have important clinical implications.

Summary—The innate immune cells contribute to both graft rejection and acceptance. Thus, a detailed understanding of the exact mechanisms and pathways that govern such opposing effects in transplant models may lead to the design of new tolerance protocols.

Keywords

NK cells; dendritic cells; tolerance; transplantation; innate immunity

Introduction

In a simplistic term, transplant rejection takes place in steps. Priming for allograft rejection requires T cells, which become activated upon recognition of alloantigens presented by donor and host antigen-presenting cells (APCs) [1]. Activated T cells then set up a complex cascade of events that eventually result in the activation and recruitment of other cell types including cells in the innate immune system to the rejection response. During this process, activated T cells as well as non-T cells mature to effector cells and acquire potent effector

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functions, which include cytolytic activities and production of effector cytokines [2]. Certain cytokines then stimulate the activation of additional immune cells that further amplify the rejection response. Finally, in the effector phase, both T cells and non-T cells that are equipped with effector activities contribute to graft destruction, when effective immune interventions are not instituted.

Despite a key role for T cells, the contribution of non-T cells to transplant outcomes has been increasingly appreciated [3]. In fact, non-T cells, especially those in the innate immune system (e.g., NK cells, DCs, macrophages), show broad impacts on graft rejection and graft acceptance depending on the models and types of tolerizing therapies used. Such cells influence the allograft response in several different ways: some innate immune cells act as inflammatory cells promoting rejection by directly damaging the graft; others regulate differentiation of T effector cells by the virtue of their cytokine production, thus affecting the nature of the rejection response or the responsiveness to tolerizing therapies. In addition, some cell types directly control T cell priming by acting as APCs whereas others promote tolerance induction by eliminating donor APCs [4]. Importantly, the cytokine milieu created by the activation of innate immune cells can be detrimental to the induction of Foxp3+ Tregs, a key cell type involved in transplant tolerance [5]. Thus, understanding precisely the role of non-T cells in transplant models and the in vivo conditions that control their pro-inflammatory and anti-inflammatory properties as well as how non-T cells interact with different subsets of T cells becomes an interesting and important issue in transplant research.

In this review article, we summarize recent advances in our understanding of the role of NK cells, macrophages, and dendritic cells in transplant models, highlighting their roles in transplant rejection and tolerance induction as well as challenges in modulating the function of such innate immune cells in the induction of transplant tolerance.

The multifaceted role of NK cells in transplant models

NK cells are innate immune cells, they are widely distributed throughput the body and frequently found in rejecting allografts, but the exact role of NK cells in solid organ transplantation has defied our understanding until recently. In various transplant models, NK cells have been shown to contribute to both allograft rejection and transplant tolerance [6], owing to certain unique features of NK cells and differences in NK functions [7].

In contrast to other immune cells, NK cells constitutively express both stimulatory and inhibitory receptors on the cell surface, and signals from both types of receptors are required to establish NK tolerance to autologous cells [8]. Interestingly, the same mechanism that induces NK tolerance to self also renders NK cells functionally competent to respond to target cells, a process called “NK licensing” [9]. The inhibitory receptors include killer-cell immunoglobulin-like receptors (KIR) in humans and the lectin-like Ly49 receptors in mice. In addition, NKG2A and CD94 usually form heterodimers on the cell surface and function as inhibitory NK receptors [10]. A remarkable feature is that the ligands for such inhibitory receptors are self MHC class I molecules, and because of this, NK cells are in a state of dominant inhibition by constantly engaging the ubiquitously expressed self MHC class I molecules. The NK activating receptors include NKp46, NKp44, and NKp30. In addition,

some KIR receptors, especially those with a short cytoplasmic domain, also deliver activating signals [11]. NKG2D is another important NK activating receptor that binds to stress-induced ligands such as Rae-1, H60, and MULT1 in the mouse. In humans, however, NKG2D binds to MIC-A, MIC-B, and ULBPs and triggers NK activation [12].

In transplant models, NK cells can readily recognize MHC incompatible allogeneic cells via “missing self” or “missing ligand” recognitions, as allogeneic cells lack self MHC class I molecules to engage NK inhibitory receptors [13]. This type of response triggers NK activation, which includes cytolytic activities and production of potent pro-inflammatory cytokines. Such “alloreactive” NK cells have been analyzed in great details in bone marrow transplant models in which NK cells promptly reject MHC mismatched bone marrow stem cells [13]. In selected models, NK cells are also involved in rejection of solid organ transplants. For example, NK cells are key effector cells in rejection of heart xenografts [14]. In addition, NK cells play a critical role in heart allograft rejection in CD28 knockout mice [15,16], they also contribute to chronic transplant vasculopathy in a hybrid resistant heart transplant model where T cell alloreactivity to the transplant is avoided [17]. It should be pointed out that in those studies, the recipient mice possess normal adaptive immune cells, thus it remains unclear whether NK cells directly mediate graft damage or indirectly by promoting the alloreactivity of adaptive immune cells or both. In immunodeficient mice (absence of T cells and B cells), NK cells by themselves fail to induce allograft rejection, but acute allograft rejection can be triggered by exposing NK cells to IL-15 [18], which is known to stimulate robust expansion and maturation of NK cells [19]. This suggests an important but conditional role for NK cells in solid allograft rejection. Several recent reports have demonstrated that NK cells can acquire “adaptive features” that are traditionally ascribed to T cells, such as the generation of memory recall responses, following IL-15 stimulation [20,21]. Hence, it remains possible that “memory NK cells” may act as potent effector cells in allograft rejection, and prevention of NK cells from acquiring “memory” phenotypes might be important in tolerance induction.

NK cells also play an unexpected role in the induction of transplant tolerance [4,22]. This initial finding was counterintuitive or paradoxical, given the role of NK cells as killers and inflammatory cells. We found that NK cells are critically important in the control of life and death of graft-derived donor cells including donor dendritic cells, and by killing donor dendritic cells through “missing self” or “missing ligand” recognition, NK cells limit the priming of alloreactive T cells in transplant recipients by the direct pathway [4]. Moreover, killing of donor cells may also facilitate the activation of T cells by the indirect pathway [23], which is considered to be permissive to tolerance induction [24]. Indeed, in the absence of NK cells, donor dendritic cells survive much better in allogeneic hosts, and in this setting, proliferation of alloreactive T cells in vivo is extremely robust [25]. This is consistent with the notion that direct stimulation of host T cells by donor dendritic cells activates a large mass of alloreactive clones [26]. In other models, NK cells have been shown to either activate self APCs or kill those that have reduced expression of MHC class I [27], thereby positively or negatively regulating immune responses. The implication of killing and activating of self APCs in transplant settings remains to be studied. There are probably other targets for NK cells. NK cells can directly inhibit or kill activated T cells [28]. Recently, NK cells have been shown to control the induction of Foxp3+ Tregs [29], which will

undoubtedly affect the status of tolerance. These studies suggest a key role for NK cells in regulating both immunity and immune tolerance through interacting with APCs and T cells, and this has important implications in the induction of transplant tolerance.

Finally, NK cells have additional attributes besides cytolytic activities and cytokine production. For example, a subset of NK cells in humans that express high levels of CD56 on the cell surface ($CD56^{bright}$ NK cells) lacks of cytolytic activities but rather produces immune regulatory cytokines that inhibit immune activation [30]. Also, activated NK cells can acquire markers of dendritic cells such as CD11c and MHC class II and function as APCs following cytokine stimulation [31]. Whether these attributes can be harnessed for the induction of transplant tolerance is unclear and remains to be studied.

Dendritic cells and transplant outcomes

Dendritic cells (DCs) are a specialized cell type in the immune system; they are well publicized as professional antigen-presenting cells critical to the commencement of immune responses [32]. We now know that DCs are required not only for immunity but also for tolerance [33]. This paradigm shift stimulates considerable interests in identifying or generating the right types of DCs that will aid in the induction of transplant tolerance [34]. In both humans and mice, various subsets of DCs have been reported, based on a combination of cell surface markers. For example, myeloid DCs are identified as $CD11c^{+}CD11b^{+}CD205^{-}$ cells whereas the lymphoid DCs are $CD11c^{+}CD205^{+}CD11b^{-}$ cells. Both subsets are also called conventional DCs that are potent stimulators of T cell proliferation. Plasmacytoid DCs distinguish themselves from others by being $CD11c^{+}B220^{+}PDCA^{+}$ cells [35]. Plasmacytoid DCs are less potent in stimulating T effector cells but appear to be more effective in stimulating Tregs. In some transplant models, plasmacytoid DCs are required for the induction of allograft tolerance [36]. In the lymphoid organs, different DC subsets are located at different sites, probably due to differential expression of chemokine and chemokine receptors as well as the homing receptors. As mentioned above, different DC subsets show differences in their ability to stimulate T effector cells and Foxp3+ Tregs, most likely due to differences in expression of costimulatory ligands and/or production of cytokines that are key to T cell activation and differentiation [37]. These differences also suggest a division of functions among DC subsets in vivo. In some studies, certain DCs are more potent than others in driving T effector cells, while in other studies, some DCs are more effective than others in the induction of Foxp3+ Tregs. However, this notion is not absolute, when DCs are further matured under inflammatory conditions, the division of functions among DC subsets is less striking, at least in vitro [38].

There are several broad approaches in modulating DCs for tolerance induction, and each has advantages and challenges [34]. The first is to create “tolerogenic DCs” in vitro and use them as cell therapies in vivo in tolerance induction. Both genetic and pharmacological means have been tried to induce and expand such cells, which include transgenic expression of coinhibitory molecules and immune regulatory cytokines in DCs or alteration in DC functions in vitro with mTOR inhibitors [39]. Depending on the models, such tailor-made DCs have demonstrated efficacy in extending graft survival when combined with other

immune interventions such as costimulatory blockade [40]. However, challenges remain, if donor DCs are used, they will be undoubtedly killed by recipient NK cells upon passive transfer [4]. In the case of using syngeneic DCs, they need to pick up the right donor antigens and deliver them in a tolerogenic form to alloreactive T cells, which is not always the case in vivo. Also, there is no way of knowing how stable of those in vitro generated DCs are in vivo, how long they survive, and whether they home to the right locations where they work the best to achieve tolerance. Another approach is to target “tolerogenic DCs” in vivo, by taking advantage of unique features of DC subsets and various tolerance induction protocols. Clearly, there is some success in this regard [36]. But challenges are equally daunting in developing an effective and clinically applicable DC targeting protocols because the alloimmunity is so dynamic and is model and context-dependent, and tolerance demands donor antigen specificity as well as durability.

Macrophages and monocytes

Macrophages and monocytes are key constituents of inflammatory infiltrates in tissue inflammation; they are also a prominent cell type in rejecting allografts [41]. Interestingly, they are extremely rare in stable transplants surviving long-term [42]. Macrophages and monocytes are rapidly recruited to sites of inflammation including allografts; they are highly responsive to cytokines such as interferons and in turn become potent producers of pro-inflammatory cytokines including IL-1, IL-6, TNF-a, which are known to enhance both innate and adaptive immune responses [43]. Such an inflammatory milieu also prevents the induction of Foxp3+ Tregs, instead it promotes differentiation of inflammatory Th17 cells [44,45]. Hence, most studies thus far suggest a pro-inflammatory role for macrophages/monocytes in transplant models. In fact, macrophages and monocytes are closely involved in graft rejection and/or resistance to tolerance induction. In an animal model of chronic allograft rejection, macrophages are shown to infiltrate the heart allografts and contribute to transplant vasculopathy [46]. In this model, partial depletion of macrophages using carrageenan reduced the severity of chronic rejection [46]. In selected clinical trials involving broad T cell depletion, some kidney transplant patients experience episodes of acute rejection even in the presence of aggressive T cell depletion therapies, and histologically, this type of rejection is associated with intense monocytic infiltrations [47], suggesting a key role for macrophages/monocytes in graft damage. It has been well recognized that aggregates of immune cells are frequently present in stable transplants with no obvious graft damage (benign infiltrates), but macrophages can turn such benign infiltrates to aggressive ones to induce graft injury. Thus, macrophages seem to control the cytopathic nature of cellular infiltrates in organ transplants.

On other fronts, some studies suggest that macrophages can have regulatory roles promoting immune tolerance. For example, when macrophages are driven to an alternatively activated state, such alternatively activated macrophages prevent autoimmune colitis by inducing and expanding Foxp3+ Tregs [48]. Whether this is also the case in transplant models remains to be determined. But a key message from this study is that a given cell type can have both pro-inflammatory and anti-inflammatory effects, depending on the models and the in vivo context of immune activation. Thus, development of strategies that can uncouple such diametrically opposite effects is therapeutically important.

Concluding remarks

Rejection, like tolerance, is incredibly complex, both innate and adaptive immune cells are intimately involved in both processes. Thus, prevention of rejection and ultimately induction of tolerance most likely requires comprehensive strategies targeting both innate and adaptive immune cells that are critically involved in the allograft response. In the past decades, we have gained a great deal of knowledge concerning the role of T cells in transplant models and devised various effective strategies to target such T cells. We are just beginning to appreciate the importance and complexity of non-T cells in graft rejection and tolerance induction, and our approaches to effectively and specifically modulate innate immune cells for tolerance induction are very much limited. This limitation hinders the creation of transplant tolerance.

Studies of non-T cells, especially the innate immune cells, will be met with challenges and surprises. The same cell type can promote transplant rejection or facilitate tolerance induction depending on models, context, and tolerizing therapies, and NK cells provide the best example in this regard. Thus, targeting such cells for the induction of transplant tolerance is unlikely to be straightforward. Apparently, depletion of such cells en-mass or inhibition of their functions globally is not ideal and may produce unwanted consequences. Thus, approaches that work well in targeting T cells may not applicable in targeting innate immune cells in transplant settings. There are several areas that require immediate attention, which include mechanisms that regulate various aspects of innate immune responses to allografts in vivo, how innate immune cells interact with each other and then regulate differentiation of effector T cells or vice versa; the impact of innate immunity on induction and stability of immune regulatory cells. These are important but under-studied areas, the potential impact of such studies on the development of better tolerizing strategies and new diagnostic and prognostic biomarkers will be significant.

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Abbreviations

APCs	antigen-presenting cells
DC	dendritic cells
KIR	Killer-cell Immunoglobulin-like Receptors
MHC	major histocompatibility complex

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* of special interest

** of outstanding interest

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